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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,184	09/26/2007	Samir Bennabi	BHC 031069	8960

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,184	BENNABI ET AL.	
	Examiner	Art Unit	
	DAVID K. O'DELL	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 10-12* is/are pending in the application.

4a) Of the above claim(s) *4 and 6-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 10* is/are rejected.

7)☒ Claim(s) *11 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/2009; 06/08/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/13430 filed 11/26/2004, which claims priority to GERMANY 103 57 510.3 filed 12/09/2003.

Claims 1-12 are pending.

Response to Restriction/Election

2. Applicant's election of Group II and the species (Example 23) and the intended use of treating hypertension in the reply filed on August 16, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that it was not pointed out which compounds read on the elected species. Claims 1-3, 5, 10-12 appear to read on the compound and claims 5, 11 read on the intended use.

Objections

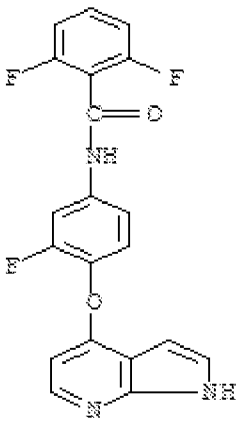
3. Claims 11-12 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 11-12 not been further treated on the merits.

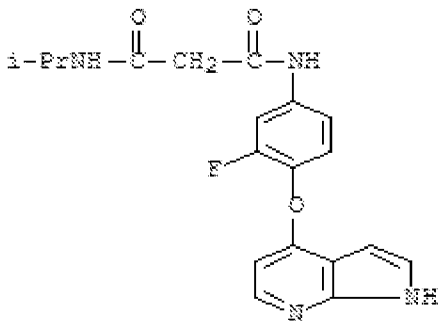
Claim Rejections - 35 USC § 102

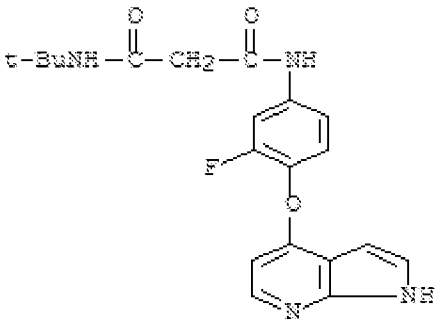
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

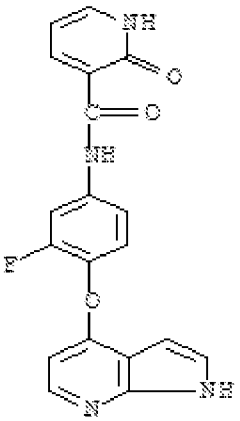
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-3, 5, 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Borzilleri et. al. US PGPub 20060004006 A1. This document teaches numerous anticipatory species including:









Some of the claims recite intended use. Intended use has no bearing on a composition of matter claim unless the use imparts a structural change, which in the instant case it does not.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The claims are extremely broad encompassing an unknown list of diseases, described only as disorders a partial list of disorders is rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease,

amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome, inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid

tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis;

and Adrenal glands: neuroblastoma and so on. Thus, the scope is broad. The elected intended use is chronic obstructive pulmonary disease.

(B) This is a compound invention but it requires the use of the intended use of prohpylaxisis and treatment of diseases and disorders. This claim is ostensibly being evaluated as a method claim.

(D) One of ordinary skill is a medical doctor.

(C) (E) The existence of a "silver bullet" for all these diseases is contrary to our present understanding of pharmacology and medicine. According to Fukata et. al. "Rho–Rho-kinase pathway in smooth muscle contraction and cytoskeletal reorganization of non-muscle cells" TRENDS in Pharmacological Sciences Vol. 22 No.1 January 2001, pgs. 32-39 (cited on the IDS) interest in Rho kinase inhibition is related to cardiovascular disorders, however the authors come to the conclusion that "Although much progress has been made, the following questions remain to be answered. First, how is the activity of the Rho–Rho-kinase pathway regulated downstream of various extracellular signals? It could involve much crosstalk with other members of Rho family GTP-binding proteins, Rac and Cdc42, and their effectors. Second, how is the Rho–Rho-kinase pathway affected in the diseases mentioned above? Third, are the disorders of the Rho–Rho-kinase pathway as observed in animal models applicable to human patients? The answers to these questions will define the physiological and pathological roles of the Rho–Rho-kinase pathway more precisely and, in doing so, help develop effective therapies for diseases caused by hypercontraction of muscle."

The instant claims embrace all diseases with distinct etiologies and different treatments including cancer. For a discussion of cancer treatment see Simone, Oncology: Introduction, *Cecil Textbook of Medicine*, 20th Edition, 1996 Vol. 1, pp. 1004-1010, states that, "each specific

type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study' (see page 1004). A tumor is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Different types of tumors affect different organs and have different methods of growth and harm to the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all solid tumors. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). Dosage regimen is dependent on several risk factors. See Trisha Gura "CANCER MODELS: Systems for Identifying New Drugs Are Often Faulty" Science 7 November 1997: Vol. 278. no. 5340, pp. 1041 - 1042:

"Indeed, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the U.S. Food and Drug Administration. "**The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all**," says Alan Oliff, executive director for cancer research at Merck Research Laboratories in West Point, Pennsylvania."

There is not even a basic causal link between many of the diseases listed and the pathway claimed. In the field of Rho kinase inhibitors any therapeutic utility is speculative at this stage and only for a very limited set of diseases.

(F) In the instant case we have been given very limited information as to what these compounds are doing in the pharmacological sense. The only information in the specification is a reference to performance in a test tube assay for inhibiting a Rho kinase enzyme, pg. 76.

(G) The application has provided no working examples of the treatment of any disease. The clinical benefit of any Rho kinase inhibitor in the diseases mentioned above has never been demonstrated.

(H) Presumably to use this invention one would need to make all the compounds of claim 1 and test them against all the various diseases in animals or humans. It is not at all clear what these compounds would do inside an organism. Based on the teaching of Fukata the complexity of Rho kinase signaling precludes conclusions based solely on enzyme inhibition alone. It is clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation.

7. Claims 1-3, 5, 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where R6 is defined as in claim 3 wherein:

R^7 represents hydrogen, halogen, cyano, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, phenyl

where alkyl, cycloalkyl, phenyl
may be substituted by amino, hydroxyl, halogen, (C_1-C_3)-alkyl, (C_1-C_3)-alkoxy or (C_1-C_6)-alkylamino,

it does not reasonably provide enablement for compounds outside of definitions of R6 in claim 3 and where

R^7 represents

5- or 6-membered heteroaryl,

or for hydrates and solvates, with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a plethora of matryoshka prophetic variables.

(B) The nature of the invention: This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as kinase inhibitors.

(D) The level of one of ordinary skill: One of ordinary skill is an organic/medicinal chemist.

(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:

Only a few examples were made and they are relatively homogenous. The R7 variable is only ever a few groups (H and methyl). The only real variation is on the groups on the R6 variable which at least for the heterocycles and heteroaryl groups, only a few were exemplified.

While some compounds outside those exemplified might be prepared by a skilled artisan, the paucity of working examples point to the key deficit in the disclosure, namely that the "how to use" requirement of 112 1st paragraph has not been met. While organic chemistry is highly unpredictable, the degree of unpredictability in the kinase inhibitor development art is even greater. The instant claims are drawn to an enormously broad recitation of prophetic moieties. The specification makes only the following statements about how compounds perform in the the kinase inhibition assay.

Example No.	IC_{50} (nM)
15	49
23	12
40	27
41	20

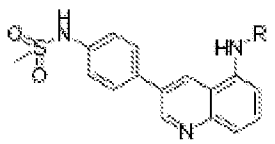
The medicinal chemistry of kinases is relatively well-developed and many limitations are well known in the art. The use of compounds as kinase inhibitors is highly dependent upon the structure of the compounds. These compounds are sensitive to structural changes that may be relatively minor in the chemical sense see, Michelotti et. al. "Two classes of p38a MAP kinase

inhibitors having a common diphenylether core but exhibiting divergent binding modes" *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 5274-5279: "In compounds of Series 2, addition of a 4-fluoro group (compound 2a) (Fig. 2) to the diphenylether results in a 2- to 3-fold increase in potency, while substituents in the 2 and 3 positions appear to be unfavorable. Removal of the phenol hydroxyl of compound 2c results in a significant loss in activity (compound 2f), suggesting that this substituent plays an important role in binding. **Modification of the sulfamide linker of compound 2c to a sulfonamide linker (compound 2h) results in a complete loss of measurable activity**."

In the instant case, very few details of regarding the choice of substituents required for activity has been given. The state of the art in the development of kinase inhibitors is highly unpredictable, See Jiang et. al. "3,5-Disubstituted quinolines as novel c-Jun N-terminal kinase inhibitors." *Bioorganic & Medicinal Chemistry Letters* **2007**, *17,* 6378-6382, where very small changes such as the removal of a halogen atom, or the position of a pyridine led to inactive compounds. Compare compounds 10c-10i to compounds 13a-13c. In the words of Jiang:

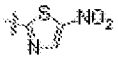
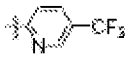
"It was surprising that the **13a** was completely inactive versus JNK3, whereas the 3- and 4-pyridyl analogs (**13b** and **13c**), though slightly better, were still considerably less active than the N-linked analogs 10a-i."

For convenience a portion is shown below:



10

Table 2. Inhibition of JNK3 by phenanthroline derivatives 10

Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
10a		0.44 ± 0.09	>20
10b		0.48 ± 0.06	>20
10c		3.6 ± 0.32	nt
10d		0.76 ± 0.15	nt
10e		13 ± 0.17	nt
10f		6.5 ± 0.53	nt
10g		0.32 ± 0.02	>20
10h		0.34 ± 0.02	nt
10i		0.49 ± 0.06	nt

[a] Values are means of three experiments; nt, not tested.

Table 3. Inhibition of JNK3 by pyridyl derivatives 13

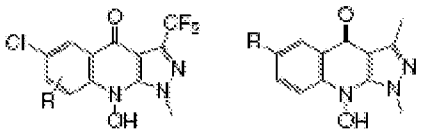
Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
13a		>20	nt
13b		5.2 ± 0.39	>20
13c		5.0 ± 0.37	>20

[a] Values are means of three experiments; nt, not tested.

See also Liu et. al. "Synthesis and SAR of 1,9-dihydro-9-hydroxypyrazolo[3,4-b]quinolin-4-ones as novel, selective c-Jun N-terminal kinase inhibitors" *Bioorganic & Medicinal Chemistry*

Letters **2006**, *16*, 2590-2594. "Analog 12a, in which chlorine was replaced with hydrogen, was not active against JNK1, whereas there was only a slight decrease in activity when chloride was replaced with bromide (10). However, replacement of chlorine by an aryl group at the same position gave only inactive compounds (12b,c). Most analogs (9a-9d) with substitution at the 5, 7, and 8 positions of the ring were inactive as well."

Table 1. Enzymatic and cellular activity of analogs with aromatic ring modifications



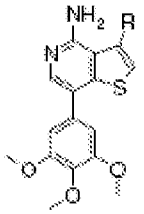
Compound	R	JNK1 IC_{50} (μM)	Pc-Jun IC_{50} (μM)
1	----	1.22	>30
2	----	0.98	16.4
10	----	0.92	>30
9a	5-Cl	>10	NT[a]
9b	7-Cl	5.14	>30
9c	8-OMe	>10	NT[a]
9d	7-$N(Me)_2$	>10	NT[a]
12a	H	>10	NT[a]
12b	Ph	>10	NT[a]
12c	1*H*-Pyrazol-3-yl	>10	NT[a]

[a] Compounds with enzymatic IC_{50}s greater than 10 μM were not tested in the cellular assay.

By changing the structure of the compound a conformational shift occurs, and rather unremarkably the ability of the compound to interact with its target is gone. See also, Miyazaki et. al. "Design and effective synthesis of novel templates, 3,7-diphenyl-4- amino-thieno and furo-[3,2-c]pyridines as protein kinase inhibitors and in vitro evaluation targeting angiogenetic kinases" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 250–254, state:

"As the data indicate, compounds with hydrophobic chloro groups regardless of substitution position (6d, 6e, and 6j) show submicromolar inhibitory activity. However, those with somewhat hydrophilic substituents such as 3-acetamido, 4-acetyl, and 4-methylsulfonyl groups (6f, 6g, and 6i) are relatively inactive. Other substituents such as 4-methoxyphenyl, naphthyl, and pyridyl provided analogues with moderate potency (6b, 6c, and 6h). The need for a phenyl group for inhibitory activity is evidenced by the lack of activity of 6a."

Table 1. EphB4 kinase enzyme inhibition of 4-amino-3-aryl-7-(3,4,5-trimethoxylphenyl)-thieno[3,2,c]pyridines 6



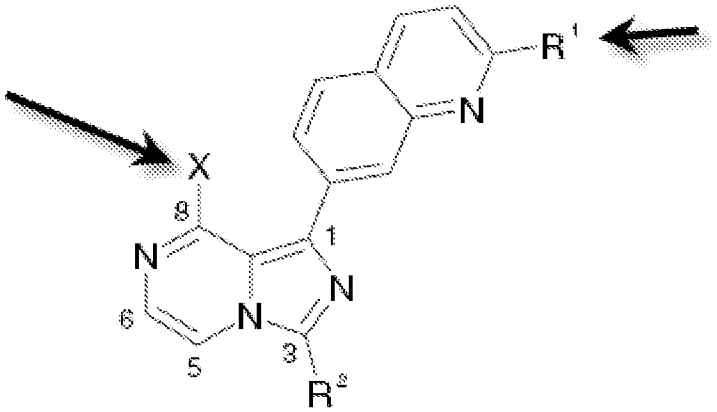
Compound	R	EphB4 IC_{50} (nM)
6a	Br	>25,000
6b	4-OMe-phenyl	7100
6c	β-Naphthyl	2200
6d	4-Cl-phenyl	190
6e	3-Cl-4-*F*-phenyl	110
6f	3-acetamide-phenyl	>25,000
6g	4-Acetyl-phenyl	>25,000
6h	3-Pyridyl	3900
6i	4-Methylsulfonyl-phenyl	>23,000
6j	2,3-Dichloro-phenyl	230

The structure activity relationships of kinase inhibitor pharmacophores have been discussed in Mulvihill et. al. "Novel 2-phenylquinolin-7-yl-derived imidazo[1,5-a]pyrazines as potent insulin-like growth factor-I receptor (IGF-IR) inhibitors" *Bioorganic & Medicinal Chemistry* **2008**, *16*, 1359–1375.

"To confirm the key pharmacophores and to test the binding model, we removed the terminal phenyl ring, replaced the cyclobutyl ring with a smaller methyl group, and also replaced the 8-amino group with a hydroxyl group, synthesizing three key compounds, 2b–c and 9, respectively. Based on the binding model, the space occupied by the terminal phenyl cannot be fully occupied by hydrophobic collapse of the nearby residues, suggesting compound 2b should

be inactive……**It was evident that the terminal phenyl ring as well as the 8-amino group, as exemplified by compounds 2b and 9, respectively, were both vital pharmacophores required for IGF-IR inhibition.** Truncation of the cyclobutyl moiety to methyl (compound 2a ! 2c) afforded a 12-fold loss in potency, highlighting that critical mass was required at the C3-position of the imidazopyrazine ring for significant IGF-IR inhibition. These data reinforced previous SAR findings from the benzyloxyphenyl series and indicates that multiple atoms in the ring make non-specific contacts with the protein."

Table 1. 3T3/hulGFIR IC_{50} values for compounds 1, 2a–c, and 9



Compound	X	R^1	R^2	IGF-IR cell IC_{50} (μM)
1	—	—	—	1.16
2a	NH_2	Ph	Cyclobutyl	0.086
2b	NH_2	H	Cyclobutyl	>10.0
2c	NH_2	Ph	Methyl	1.04
9	OH	Ph	Cyclobutyl	>10.0

The same author shown that for this pharmacophore, the activity is governed by the interaction of the compound with key residues of the IGF-IR protein. Mulvihill et. al. "1,3-Disubstituted-imidazo[1,5-a]pyrazines as insulin-like growth-factor-I receptor (IGF-IR) inhibitors" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 1091–1097.

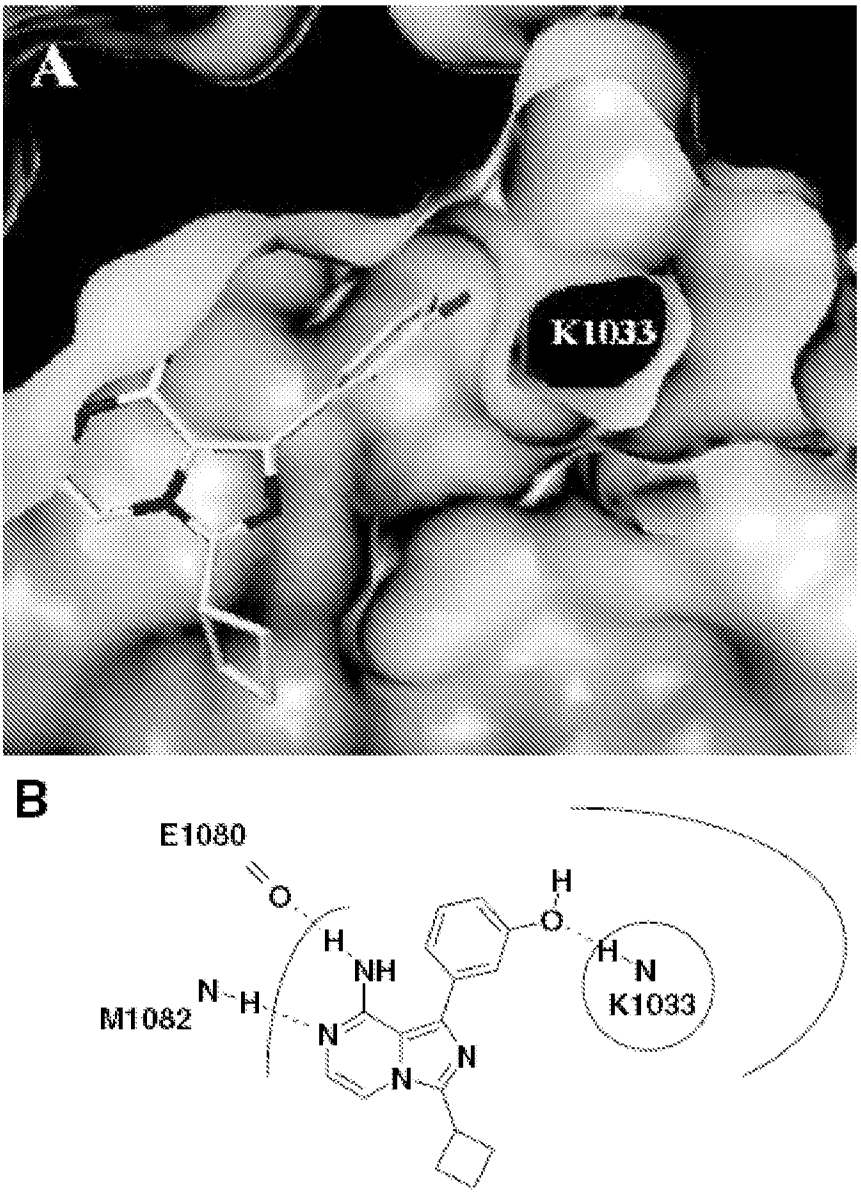


Figure 2. (A) Surface display of a model of the ATP binding pocket with compound 6a.6 bound. The surface is colored by depth from shallow/solvent-exposed blue to deeply buried orange. The hole in the surface is the space carved out by K1033. A small space 'behind' K1033 is visible. (B) 2D representation of Figure 2A, highlighting the key interactions in the site. The basic amine of K1033 makes a key hydrogen bond with the hydroxyl. Canonical hinge binding interactions are also present.

Kinase active sites are highly conserved amino acid sequences across several classes. The compounds are generally mimics of the natural enzyme substrate ATP, such that a compound that is too large and has all of these prophetic groups hanging off of it simply won't fit into the enzyme active site or allow for the very subtle interactions required for inhibition. In this case the prepared compounds bear a structural resemblance to one another, yet the claims are not commensurate in scope.

With respect to the solvates, the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

a) Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, pressures, and humidity. The experimentation is potentially open-ended. b) The direction concerning the hydrates is not found in the specification c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they

would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

d) The nature of the invention is chemical synthesis, which involves chemical reactions.

e) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate/hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. f) The artisan using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as

well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only four working examples in this unpredictable art without undue experimentation.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID K. O'DELL whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JANET ANDRES can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David K. O'Dell/
Examiner, Art Unit 1625